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09/464,414	12/16/1999	YASMIN THANAVALA	RPP:156CUS	7502

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	

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09/464,414

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Attached hereto is an initialed copy of the "Information Disclosure Statement by Applicant" filed on December 16, 2002.

MICHELE FLOOD
PRIMARY EXAMINER

Michele Flood
Primary Examiner
Art Unit: 1655

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 0104

Application Number: 09/464,414
Filing Date: December 16, 1999
Appellant: THANAVALA, YASMIN

Michael L. Dunn
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 23, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct, with the exception for the rejection made under 35 U.S.C. 112, second paragraph, and the rejection made under 35 U.S.C. 103, which have been withdrawn.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Evidence Relied Upon

5,654,184	CURTIS, III et al.	8-1997
5,679,880	CURTISS et al.	10-1997
5,686,079	CURTISS et al.	11-1997
5,914,123	ARNTZEN et al.	6-1999
6,136,320	ARNTZEN et al.	10-2000

Bratu et al. "Active Immunization Against Human Tick-Borne Diseases". Expert Opinion Biological Therapy (2002), Vol. 2, No. 2, pp 187-195.

Titball et al. "Vaccination Against Bubonic and Pneumonic Plague", Vaccine (2001), Vol. 12, No. 20, pp 4175-4184.

(10) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims:

Claims 1-3, 7, 9, 10 and 13 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for providing a secondary boosting immune response in a mammal to a non-enteric pathogen antigen (NEPA), wherein the NEPA is hepatitis B surface antigen (HBsAg) comprising the instantly claimed process steps and instantly claimed ingredients, does not reasonably provide enablement for providing a secondary boosting immune response in a mammal to any and all NEPAs comprising the instantly claimed ingredients. The specification does not enable any person skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention. This rejection is set forth in prior Office Action, which is dated April 22, 2003, as set forth immediately below.

A method for providing a secondary boosting immune response in a mammal to a specific antigen of a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not itself enterically raise a primary protective immune response in mammals in the absence of prior acquired immunity to the pathogen, said method comprising: rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection; and then orally administering the NEPA to the immunoreceptive mammal by feeding the mammal with transgenic potato containing the NEPA expressed in the potato to enterically cause a secondary immune response to the oral administration specific to the NEPA stronger than would be caused

by orally administering the NEPA in the absence of the prior immunization by injection is claimed. Dependent claims recite the claimed method wherein the mammal is a human; wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever; wherein the human ingests sufficient plant material to provide from about 10 to about 100 micrograms of NEPA per kilogram of body weight of the human; wherein the human ingests sufficient plant material to provide from about 2 to about 5 grams of plant material per kilogram of body weight of the human; wherein the human ingests the plant material a plurality of different times, the times being separated from each other by at least 5 days; and, wherein the plurality of times is three times.

The specification broadly discloses non-enteric pathogens that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin, *e.g.*, blood transfusions which can be used as sources of NEPA to raise a protective enteric immune response in mammals. However, the specification does not provide sufficient guidance as to how one of ordinary skill in the art would provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. The specification does not disclose other specific non-enteric pathogen antigens which have been subjected to the claim-designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than

the non-enteric pathogen antigen, hepatitis B surface antigen. In regard to Claim 1, the specification, other than the mere suggestion on page 1, lines 13-16, does not provide guidance as to how to use the instantly claimed invention to provide a secondary boosting immune response to any and all diseases caused by a non-enteric pathogen that invades the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin. Moreover, there is inadequate guidance as to how one of ordinary skill in the art would use the instantly claimed invention to genetically alter potato plant material to express any and all non-enteric pathogens other than the exemplified HBsAg for use in the claim-designated method for raising the immune response in a mammal and/or human when administered orally.

In view of prior art teachings, the Office deems that one skilled in the art would know how to "cause a plant to express a viral immunogen (antigen)", *i.e.*, to make a genetically altered plant material which expresses a NEPA or pathogenic microorganism. However, the Office does not find that at the time invention was made one skilled in the art would know how to make and/or use the claim-designated plant material, *i.e.,* the potato, to express any and all NEPAs to provide the instantly claimed method, except for those demonstrated by Applicant, or disclosed by the teachings of the cited prior art (*see* Tables in Columns 13-14 in U.S. 5,914,123 and U.S. 6,136,320).

The art of virology, microbiology, and immunology are highly unpredictable because there are too many unknowns in the claimed process for the skilled artisan to be enabled to practice the invention commensurate in scope to the claimed invention. Effective treatments for providing immunological responses to the disclosed pathogens

are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to methods for the administration of compositions to mammals and/or humans generally require supporting evidence which clearly define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, Applicants would have to demonstrate the functional effect and describe the effective amounts of each ingredient for the administration of the composition or compositions intended for a therapeutic treatment. Accordingly, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed plant materials expressing a non-enteric pathogen selected from those pathogens which cause the diseases hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever, other than the demonstrated hepatitis B, to provide the claimed functional effect to cause a secondary immune response in a mammal, wherein the specific immune response to the NEPA was stronger than would be caused by the NEPA in the absence or prior immunization by rejection upon oral administration of the NEPA.

(11) Response to Argument

With regard to the rejection of Claims 1-3, 7, 9-10 and 13 made under 35 U.S.C. 112, first paragraph, Applicant argues that the rejection should be reversed. Applicant's main argument is directed to the idea that the specification provides clear enabling support for the claimed invention, especially as it applies to the NEPAs selected from the group as set forth in claim 3, namely, hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever, when considered in conjunction with the knowledge of one skilled in the art. Applicant further argues, "One skilled in the art clearly knows how to make the required genetically altered plant material and in the 35 U.S.C. 103 rejections discussed infra, the Examiner has relied upon cited patents that clearly teach how to make the required plant materials and patents cited by the Examiner in fact have generically claimed such plant materials." Thus, Applicant points to U.S. Patent 5,679,880, U.S. Patent 5,686,079, U.S. Patent 5,654,184, and U.S. Patent 6,136,320 to support the position that one of skill in the art at the time the invention was made would have known have to make and/or use a transgenic plant, comprising and expressing a DNA sequence coding for an antigen of a pathogenic microorganism or an antigenic determinant thereof to elicit a secretory immune response in a human or other animal upon oral administration of the tissue of the transgenic plant. The Office concedes that one skilled in the art at the time the invention was made would have known how to make and/or use a plant to express a viral immunogen (antigen) for the oral administration thereof to elicit an immunogenic response, such as the viral immunogens

disclosed therein the cited patent literature. However, Applicant's argument that the claimed invention can be used to provide the claimed beneficial effect for providing a secondary boosting immune response in a mammal to a specific antigen of any and all NEPAs comprising the instantly claimed ingredients and claimed process steps is not persuasive because Applicant has not provided sufficient guidance as to how one of either ordinary skill in the art or one of skill in the art would render a mammal immunoreceptive to an antigen of any and all non-enteric pathogens using the claimed method, which encompasses the instantly disclosed process steps and ingredients. On page 5 of "REVISED APPEAL BRIEF", line 18 to page 6, line 1, Applicant argues, " . . . it has been unexpectedly discovered that immunogens from non-enteric pathogens can be included that do not raise an oral primary immune response but can be used to obtain a secondary oral immunogenic response, if the animal is first vaccinated (non-orally)." As the claimed method is a two-step process, each steps needs to be satisfied or realized to accomplish the beneficial functional effect for providing a secondary boosting immune response in a mammal to a specific antigen of a non-enteric pathogen. In the instant case, Applicant has not provided sufficient guidance as to how either one of ordinary skill in the art or the skilled artisan would make and/or use the claimed invention, especially since Applicant has not provided sufficient guidance as to how one of skill can render a mammal immunoreceptive to an antigen of any and all non-enteric pathogens by prior immunization via vaccination by injection, wherein the vaccination contained the NEPA.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation added to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

As set forth in the previous Office action , the Office maintains that the art of virology, microbiology, and immunology are highly unpredictable because there are too many unknowns in the claimed method for the skilled artisan to be enabled to practice the invention commensurate in scope to the claimed invention, despite Applicant's argument to the contrary. Full consideration was given to each of the patent and non-patent literature cited by Applicant to support the position that the present invention is fully enabled with respect to non-enteric pathogen antigens other than the HBsAg demonstrated by Applicant. While it is true that a patent specification is not intended to be a textbook including all information known and readily available to a skilled person, it is also true that the information at the time of filing should be known and readily available for the practitioner to practice the claimed invention. For example, effective immunization treatments for providing immunological responses in mammals, much less humans, to the disclosed non-enteric pathogens are moderately rare, controvertible, and in some instances unsafe; and, therefore, may be unbelievable in the absence of

supporting evidence. It should be noted that the state of the art at the time of filing suggests that the functional effect for rendering a mammal immunoreceptive to any and all NEPAs by prior immunization via vaccination by injection, as broadly claimed by Applicant, was atypical or not available. Moreover, with regard to the claim-designated disease conditions as set forth in Claim 3, at the time the invention was filed, it was generally not accepted or firmly established in the art that mammals could be rendered immunoreceptive to each of the antigens specific to the non-enteric pathogens that cause the disease conditions of hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever by prior immunization via vaccination by injection, as evidenced by the teachings set forth immediately below. Firstly, on page 191, column 1, Bratu et al. (Expert Opinion Biological Therapy, 2002, 2(2): 187-95, Active immunization against human tick-borne diseases, under *"4. Rocky Mountain spotted fever immunization"*) teach, "Currently there is no licensed vaccine available for protection against *R. rickettssi* . . .". Bratu further teaches that a vaccine developed against *R. rickettssi*, the etiological agent that causes spotted fever, provides only limited immunity when administered to either animals or humans. Secondly, Titball et al. (Vaccine, 2001, 12(20): 4175-84. Vaccination against bubonic and pneumonic plague) teach that while both live attenuated and killed whole cells vaccines have been used in the immunization of man against *Y. pestis*, the etiological agent that causes bubonic plague, "there is circumstantial evidence for the efficacy of these vaccines." *See* entire document, especially, page 4177-4182. Thirdly, in *"Genetically Modified*

Vaccines: Vaccines by Design" (Current Pharmaceutical Biotechnology, 2001, 2: 47-76), Stephenson teaches, "there is still no commercially available dengue vaccines", on page 49, column 2, line 20-30. Note that in Table 2, on page 49, Titball also teaches that there is no commercial available vaccine against the Rotavirus: "*A commercial vaccine has been produced, but has recently been withdrawn due to an unacceptably high incidence of intusseption in vaccines" and, on page 71, column 1, lines 24-31, Titball concludes, " . . . there is still no vaccine against dengue fever, herpes, rotaviral diarrhoea, pneumonia caused by respiratory syncitial virus or hepatitis C." *See* also Farci et al. (Science, 1992, 258: 135-140. *Lack of Protective Immunity Against Reinfection with Hepatitis C Virus".*), wherein Farci reports various mechanisms that hamper the development of injectable vaccines against Hepatitis C for effective immunization therapy in mammals. In view of the teachings of Bratu, Titball, Stephenson and Farci, the Office maintains that the specification does not provide sufficient guidance as to how one of ordinary skill in the art would have know how to practice the claimed invention to the extent of the breadth of the claims given the disclosure of the specification, and in view of the teachings of Bratu, Titball, Stephenson and Farci, which teach that at the time of filing of the claimed invention it was not known in the art to immunize mammals against any and all non-enteric pathogen antigens that cause disease conditions, such as those recited in Claim 3, by injectable vaccines.

In order to enable the skilled artisan to practice the invention as claimed, Applicant would have to demonstrate the functional effect and describe the effective amounts of each ingredient intended for a therapeutic treatment. Given the limited

disclosure of the claimed invention as set forth in the specification and the state of the art at the time the invention was filed, other than the aforementioned demonstrated method , it would take undue experimentation without a reasonable expectation of success to provide a secondary boosting immune response in a mammal to any and all non-enteric pathogen antigens comprising the instantly claimed process steps and instantly claimed ingredients.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

MCF
January 9, 2004

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